Effect of Bispectral Index-Guided Total Intravenous Anesthesia on Post-Anesthetic Recovery Outcomes in High-Risk Children: A Prospective, Randomized, Controlled Trial

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Abstract

BACKGROUND

TIVA is widely used in children, but few studies have attempted to evaluation of the effect of BIS-guided propofol infusion than that on conventional methods on recovery outcomes in children with higher risk factors.

OBJECTIVE

To evaluate the effect of bispectral index (BIS) guidance during total intravenous anesthesia on post-anesthetic recovery outcomes in children at higher risk during anesthesia.

DESIGN

A prospective, randomized, controlled trial.

SETTING

University medical centre.

PATIENTS

This study enrolled 472 children (aged 1-14 years) who met the higher-risk scoring criteria and were scheduled for surgery under total intravenous anesthesia.

INTERVENTION

The children were randomly assigned to the BIS group (group B) and standard clinical practice group (group S). The BIS values in group B were maintained at 45–60. The anesthesiologist controlled the depth of anesthesia in group S according to the variation in the clinical signs of the children.

MAIN OUTCOME MEASURES

BIS values, heart rate (HR), mean arterial pressure (MAP), and pulse oxygen saturation at each time points, as well as the time between drug withdrawal to extubation, duration of stay in the post-anesthesia care unit (PACU), the total amount of propofol used, and postoperative adverse reactions were recorded.

RESULTS

There was no significant difference in time from stopping propofol infusion to extubation and duration of PACU between the groups . There was no significant difference in BIS values between the groups at T2, T3, and T8. BIS values at T1, T4, T5, T6, and T7 in group B were lower than those in group S. There was no statistically significant difference in the HR between the groups. MAP in group B was lower than in

group S at T5, T6, T7, and T8. The total amount of propofol administered in group B was higher than in group S.

CONCLUSION

The use of BIS-guided total intravenous anesthesia in higher-risk children can maintain the proper depth of anesthesia but does not prolong the time of extubation and the duration of stay in the PACU.

TRIAL REGISTRATION

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Background

Compared to inhalation anesthesia, total intravenous anesthesia (TIVA) may present clinical advantages. Recent studies have demonstrated that propofol anesthesia in children, as in adults, is associated with a major reduction in post-anesthetic nausea and vomiting incidence,[1] with a decrease in emergence agitation episodes[2] and a better quality of recovery.[3] In addition, TIVA is widely accepted by anesthesiologists because it reduces passive inhalation by anesthesiologists. Currently, the latest application method of TIVA involves using a target-controlled infusion pump to induce and maintain anesthesia. However, the pump is not available in all countries and hospitals; therefore, a manual infusion regimen based on varying infusion rates is widely used in children.[4] The dose and speed of manual infusion are judged and adjusted by pediatric anesthesiologists according to the clinical parameters of the children. Because many factors interfere with clinical parameters, it is difficult to adjust the anesthesia depth objectively, quantitatively, and accurately. Therefore, continuous propofol infusion under the guidance of BIS or other monitoring indexes has gradually gained application in pediatric anesthesia. Previous studies have shown that propofol combined with remifentanil infusion under auditory-evoked potential monitoring can reduce propofol consumption and time to the emergency.[5] Still, studies show that BIS-guided propofol infusion has no advantage over conventional anesthesia in propofol consumption and emergency times.[6] Regardless of the results of previous studies, there are still fewer studies on the effect of BIS-guided propofol infusion than that on conventional methods on recovery outcomes in children with higher risk factors, including younger age, longer operative time, more bleeding, and higher American Society of Anesthesiologists (ASA) grade.

The objective of this prospective, randomized, controlled study was to evaluate the effects of BIS monitoring on recovery from anesthesia in higher-risk children undergoing elective surgery, using BIS-guided continuous infusion of propofol and remifentanil compared with the conventional anesthesia method.

Methods

Ethical approval and consent to participate

This study was approved by the Ethical Committee of Beijing Children's Hospital, Capital Medical University, National Center for Children's Health with approval number 2016-99. The patient`s parents provided written consent. All the experiment protocol for involving human date and methods were in accordance with the guidelines of Declaration of Helsinki.

Study Population

From June 2016 to June 2019, a total of 472 children undergoing elective operations, such as urologic, orthopedic, and surgical oncology procedures, under general anesthesia were consecutively enrolled. The inclusion criteria were as follows: children who received endotracheal intubation or laryngeal mask insertion under TIVA, whose ages were between 1 to 14 years, and whose ASA scores were I to IV. Whether the children were at higher risk or not was assessed according to ASA grade, age, estimated operative time, and intraoperative blood loss. The specific scoring criteria are listed in Table 1. Children with a score greater than or equal to 4 were enrolled. The exclusion criteria were as follows: children with intraoperative use of inhaled anesthetics, those who underwent cardiopulmonary bypass surgeries for congenital heart disease, craniocerebral surgeries, where BIS electrodes could not be placed, and surgeries with an estimated operative time < 60 min. Children with a history of nervous system disease, use of related medications, and a history of allergy to the study drug were likewise excluded. Children were randomized into the BIS group (group B) and the standard clinical practice group (group S) using SAS 9.4 software, with 236 children in each group. The anesthesia depth of children in group B was accurately adjusted according to the BIS value. The anesthesia depth of children in group S was adjusted according to the judgment of the clinical parameters by the anesthesiologist.

Table 1
Scoring scale for enrollment of high-risk children

Item	0 points	2 points	4 points
ASA grades	Grade I-II	Grade III	Grade≥IV
Age	6≤age≤14	3≤age≤6	1≤age≤3
estimated operative time	<2 hours	2–4 hours	>4 hours
Estimated intraoperative blood loss	<10% TBV	10-20% TBV	≥20% TBV
The inclusion score is calculated by summing the scores of the four items; children with a score ≥4 can be included.			

Anesthesia Method

None of the patients were pre-medicated. Children were routinely fasting from food for ≥6 h and from drinking for ≥2 h before surgery. Peripheral intravenous access was established in all patients in the hospital ward. A continuous monitor (MP70 monitor; Philips Intellivue, Germany) was used for

noninvasive blood pressure, pulse oxygen saturation, heart rate (HR), and electrocardiogram monitoring in the operating room. BIS electrodes were attached to the forehead of the child, and a BIS monitoring instrument (Aspect Medical System, USAB) was connected and continuously monitored.

All children underwent induction with 2-3 mg/kg of propofol (1% propofol in a medium-chain/long-chain triglyceride emulsion; Fresenius Kabi Deutschland Gmbh, Germany), 0.2–0.3 μg/kg of sufentanil (Yichang Humanwell Pharmaceutical Co., Ltd., Hubei Province, China) or 2–3 μg/kg of fentanyl (Yichang Humanwell Pharmaceutical Co., Ltd., Hubei Province, China), 0.5–0.7 mg/kg of rocuronium (Hameln Pharmaceuticals Gmbh, Germany), followed by endotracheal intubation or laryngeal mask placement after a sufficient depth of anesthesia was achieved. After intubation, the anesthesia machine (Datex-Ohmeda Inc., Madison, USA) was connected to maintain mechanical ventilation, with a tidal volume of 8–10 ml/kg, a frequency of 15–20 beats/min, and I: E=1:2. An intravenous injection pump (Smiths Medical Instrument Co., Ltd., Zhejiang Province, China) was then connected for continuous intravenous infusion of propofol 4–12 mg/kg/h and remifentanil (Yichang Humanwell Pharmaceutical Co., Ltd., Hubei Province, China) 0.2–0.4 μg/kg/min to maintain anesthesia. For pediatric patients in group B, the anesthesiologist adjusted the infusion rate of propofol according to the BIS values and tried to keep the BIS values between 45 and 60. Pediatric patients in group S were also monitored for BIS, but the anesthesiologist was blinded to the BIS value, and the research nurse recorded the BIS value. The anesthesiologist controlled the anesthesia depth according to routine methods of HR, BP, and surgical simulation. After skin closure, all anesthetic infusions were discontinued, and the endotracheal tube or laryngeal mask could be removed when the child's protective reflexes such as choking and swallowing were restored. There was an eye-opening reflex by patting the cheek. The patients were sent to the post-anesthesia care unit (PACU) and continued to be observed and evaluated by the nurses who were unaware of the study design and grouping in the recovery room. The patients could return to the ward only after the total score of the three items was above 4 points (A + B + C ≥ 4 points). The Steward Awakening Score Scale[7] is presented in Table 2.

Table 2
Steward awakening score scale

		2	1	0
A	Level of consciousness	Full recovery	Responsiveness to stimulation	No responsiveness to stimulation
B	Degree of the unobstructed respiratory tract	cough on request	Maintenance of respiratory tract unobstructed without support	Requirement for respiratory support
C	Physical activity	Moving of limbs purposefully	Non-purposeful moving of limbs	No motoric activity of limbs

Data Collection

After admission, the BIS (Aspect Medical Systems, USA) was simultaneously monitored for all patients. According to the manufacturer's instructions, the skin over the forehead was cleaned, and the anesthesiologist placed the BIS electrode. The BIS monitor requires a self-test before it begins to function. The same nurse recorded the BIS values, corresponding heart rate, blood pressure, and pulse blood oxygen saturation values at 1 min before induction (T1), 1 min after induction (1 min after the induction drugs were administrated) (T2), immediately after intubation (T3), immediately after skin incision (T4), 30 min after the start of the operation (T5), 60 min after the start of operation (T6), immediately after drug withdrawal (T7), and immediately after extubation (T8). Furthermore, she recorded the time of extubation (the time from stopping all anesthetic infusions to the removal of the endotracheal tube or laryngeal mask) and the duration of stay in the PACU (the time from being transferred to the PACU after extubation to meet the criteria for leaving the recovery room). At the time of data collection, the anesthesiologist observed the BIS values in group B but not by the anesthesiologist in group S. The time of extubation, duration of stay in the PACU, and the total amount of propofol administered was recorded. The incidence of anesthesia-related adverse reactions within 24 hours and adverse events within 1 month after the operation was observed and followed up.

Randomization

Stratified randomization with anesthetist as stratum will be performed. The randomization number will be generated by the statistical professionals using SAS 9.4. .Each subject who qualifies for entry into the study will be assigned a patient number according to the time order. Each anesthetist will be provided with a randomization list (using blocks). Then, a patient scheduled for surgery would be first assigned to an anesthetist and then randomized to the study group. Each number corresponds to the randomization and allocates the subject to one of the groups (1:1 group allocation).

Blind Method

This study is a single-blind trial. The subjects of both groups will accept continuous BIS monitoring, and will not know whether they belong to the study group or the control group before or after anesthesia. During the anesthesia process, the investigators conduct the anesthesia guided by BIS and that guided by standard practice respectively in accordance with the group situation. To ensure the objective assessment, the statistical staff also will not know the details of grouping details.

Statistical analysis

The sample size was calculated based on previous similar literature results,[8] with the time of extubation being the primary outcome measure. The case ratio of the experimental group to the control group was 1:1, and the independent sample *t*-test method was used in the case of $\alpha = 0.025$ (two-sided), power (1-

β)=90%. The calculation result of the sample size was 165 children in each group, and the estimated dropout rate was 30%. Therefore, the sample size of this study was approximately 236 per group, with a total of 472 children.

IBM SPSS (version 21.0; SPSS Inc., Chicago, IL, USA) was used for data analysis. Normally distributed numerical data are expressed as mean ± standard deviation (SD; x±s), and the comparison between the two groups was performed using an independent-samples t-test. The measurement data of skewed distribution were expressed as the median. Rank-sum tests for independent sample comparison were used, and more than three groups of measurement data were analyzed by repeated-measures analysis of variance. The count data were expressed as a percentage, and the χ^2 test was used for inter-group comparisons. Statistical significance was set at $p < 0.05$.

Results

Fifty-eight of the 472 enrolled children were excluded. Twenty-three patients in group B were excluded, including 19 patients whose operative time was less than 1 h, 1 patient who was intraoperatively treated with sevoflurane, one patient with early reduction of infusion pump drugs, and two patients whose excessively long operative time imposes serious bias on the statistical data. Thirty-five patients in group S were excluded, including 33 patients whose operative time was less than 1 h, 1 patient who was intraoperatively treated with sevoflurane, and one patient whose muscle relaxant was not administered at induction. A total of 414 children were enrolled: 213 in group B and 201 in group S (Fig. 1). General information of the two groups of children is shown in Table 3, and there was no statistical difference in sex, age, weight, and operation type (P>0.05). There was no significant difference in extubation time, duration of stay in the PACU, and anesthesia time between the two groups (P>0.05). There was a significant difference in the total amount of propofol consumed between the two groups (P<0.05), and group B consumed more propofol than group S (Table 4). In addition to time points T2, T3, and T8, the BIS values in group S were significantly higher than those in group B at other time points (P<0.05), as shown in Fig. 2. There was no statistically significant difference in heart rate between the two groups (P>0.05), as shown in Fig. 3. There was a statistically significant difference in MAP between the two groups at T5, T6, T7, and T8; MAP in group B was lower than in group S, and P<0.05, as shown in Fig. 4. No serious anesthetic-related adverse reactions or complications were found in the two groups during the operation, 24 hours, and 1 month after the operation.

Table 3
Comparison of characteristics between Bispectral Index (B) and Standard of Care (S) groups

Groups	B (n=213)	S (n=201)	Z value	P value
Sex (male/female)	166/47	159/42	—	0.811
Age (years)	2 (1,2)	1 (1,2)	-1.440	0.150
Weight (kg)	12 (11,14)	12 (10,14)	-1.700	0.089
Surgey type				
Urologic	144	140		
General surgery	29	25		
Oncologic	16	15		
Orthopedic	19	16		
Others	5	5		
P>0.05				
Median (25%, 75%)				

Table 4
Anesthesia time, extubation time, duration of PACU stay, and total propofol administered in the Bispectral Index (B) and Standard of Care (S) groups

Groups	B (n=213)	S (n=201)	Z value	P value
Anesthesia time (min)	116 (87,151)	116 (84,151)	-0.662	0.508
Extubation time (min)	15 (10,20)	14 (11,20)	-0.006	0.995
Duration in PACU (min)	27 (20,35)	29 (22,39)	-1.521	0.128
Total amount of propofol administered (mg)	303 (229,421)[a]	270 (219,368)[a]	-2.313	**0.021**
[a]P>0.05				
Median (25%, 75%)				

Discussion

In this study, after performing a comparison between BIS-guided TIVA and TIVA in which the anesthesia depth was determined with reference to clinical indexes in children with higher risk during anesthesia, it was found that the use of BIS monitoring in TIVA in children with higher risk during anesthesia can

maintain proper intraoperative anesthesia depth without prolonging the time of extubation and the duration of stay in the PACU.

This study used a manually controlled infusion pump instead of a target-controlled infusion (TCI) pump. Although there are currently some studies on the reliability of target-controlled infusion of propofol in children,[9] there are studies showing that there are distinct differences in the time to reach the expected BIS value in different target-controlled infusion modes eye-opening time, and time of extubation.[10] In addition, the results showed that there was no significant difference in the administration of propofol between manually-controlled infusion and target-controlled infusion of propofol, indicating that manually-controlled infusion of propofol is a feasible method for children.

The results of retrospective studies conducted by Carlos et al. demonstrated that using BIS monitoring in adult general anesthesia operations could reduce extubation, time of awakening, duration of stay in the operating room, and PACU. It can also reduce postoperative nausea and vomiting, cognitive dysfunction within 3 months after the operation, postoperative delirium, intraoperative awareness, and adverse events related to anesthetic medications.[11] The results of a study conducted by Bhardwaj et al. showed that BIS-guided propofol infusion in children was not superior to the conventional anesthesia method in anesthetic consumption and recovery time,[6] and the study conducted by Bresil et al. on continuous infusion of propofol and remifentanil with BIS monitoring in children or adults showed similar results. It was concluded that continuous infusion of propofol and remifentanil with BIS monitoring could not reduce the amount of anesthetic used and the time of extubation in children or adults.[12] The results of our study showed that there was no statistically significant difference in the time of extubation and duration of stay in the PACU between the BIS monitoring group and the standard clinical practice group, which was different from that of the adult study by Carlos et al.[11] but consistent with that of a previous study on children by Bhardwaj et al..[6] There was a statistically significant difference in the total amount of propofol administered in our study. The total amount was greater in the BIS group than in the standard clinical practice group. This result was inconsistent with the findings of previous studies on children by Bhardwaj et al. and Bresil et al..[6,12] The reason may be that the above previous studies were conducted in children with ASA scores ranging from I to II, while our study was aimed at children with higher risk during anesthesia. The anesthesiologist in the standard clinical practice group was relatively cautious when administering the drug. This result was also consistent with those reported in previous literature, showing that there could be a higher risk when manually controlled infusions were conducted using only clinical signs as reference indexes.[9]

The results of studies conducted by Tschiedel et al. showed that when the BIS was less than 60, good sedation could be provided during anesthesia in children, intraoperative awareness could be reduced. The depth of anesthesia sedation could be adjusted at any time according to the BIS value to prevent drug overdose.[13] In this study, the BIS values of children in the BIS group were consistently below 60 during anesthesia at T2-T7, maintaining a good depth of anesthesia, while the BIS values of children in group S were all ≥60 at T4-T7. The difference between the two groups was statistically significant. In terms of

clinical signs, although there was no statistically significant difference in heart rate between the two groups, the mean arterial pressure in group S was at a high level from half an hour after the start of the operation to immediately after extubation, which was significantly different from that in the BIS group. The results of previous studies in children showed that there was no statistically significant difference in blood pressure, heart rate, and BIS value between the BIS monitoring group and the standard clinical practice group during anesthesia.[6,12] Although one study has shown that the BIS values of children aged 1-11 during anesthesia were higher than 60, that may be due to no muscle relaxant.[12] Based on the analysis of the results of the BIS value and mean arterial pressure, it was considered that this was because the anesthesiologist in group S was relatively cautious while administering drugs in children with higher risk during anesthesia. Therefore, there may be a risk of intraoperative awareness if there is shallow anesthesia in group S. These results further explain why the consumption of propofol in group B was larger than that in group S. Nevertheless, there was no difference in the time of extubation between groups B and S, indicating that TIVA with BIS monitoring was superior to the method used in the standard controlled group.

In this study, the mode of continuous infusion of propofol and remifentanil was intraoperatively used. A study has shown that remifentanil can reduce the cardiac index (CI) and increase the plasma concentration of propofol. However, it had no obvious effect on the BIS value.[14] Therefore, during the operation, in group B, the anesthesia depth was adjusted by changing the dose of propofol according to the BIS value, while in group S, the depth was adjusted according to the clinical signs.

Limitations

There were some limitations to this study. First, the age range of the children was 1-14 years. However, the number of children meeting the inclusion criteria for older children was very limited in the actual case collection process. Most of the children were aged between 1 and 6 years, which may lead to selection bias. However, there was no statistically significant difference in the age of the children between the two groups. Second, because of younger age, no investigation of intraoperative awareness was performed in the selected children. Therefore, in shallow anesthesia, it can be speculated that there is a possibility of intraoperative awareness. This is also the focus of our future research.

Conclusions

In conclusion, in higher-risk children, TIVA with BIS monitoring can maintain appropriate intraoperative anesthesia depth without prolonging extubation and time in the PACU, which has several advantages, from improving perioperative safety to the possibility of adjusting anesthesia depth according to clinical signs.

Declarations

Ethics approval and consent to participate: This study was approved by the Ethical Committee of Beijing Children's Hospital, Capital Medical University, National Center for Children's Health with approval number 2016-99. The patient`s parents provided written consent. All the experiment protocol for involving human date and methods were in accordance with the guidelines of Declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: All authors have read and approved the final version of this manuscript. FW contributed to the overall study design, data analysis and revised the paper. JZ helped design the study and revised the manuscript. GL helped design the study, performed the experiments, analyzed the data, and wrote the previous versions of the manuscript. LL, XW, LH, XZ, CZ, JG, and WH performed the experiments and collected the data.

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Figures

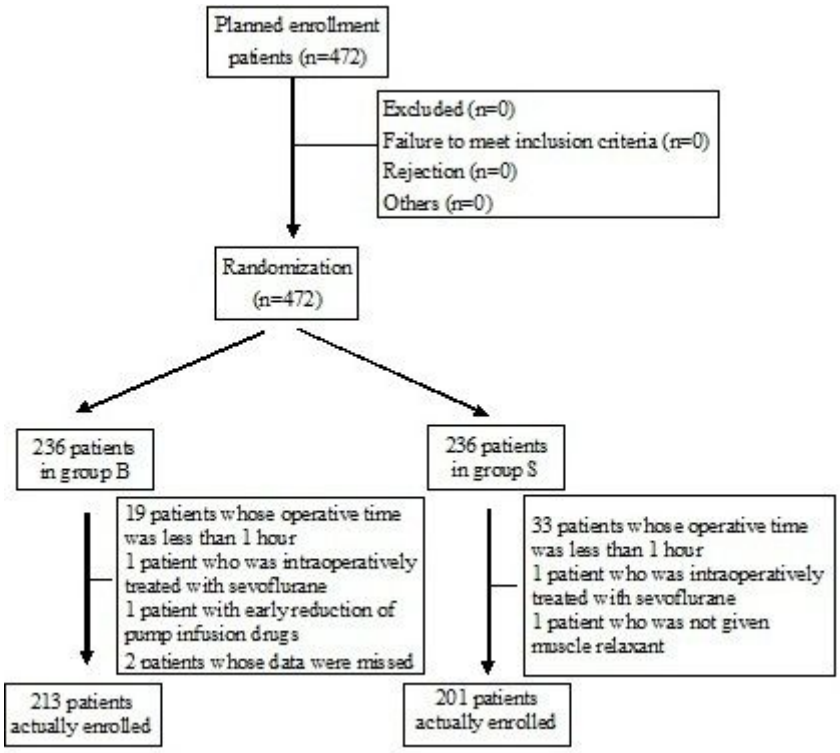

Figure 1

Flowchart showing the process of enrollment of all children

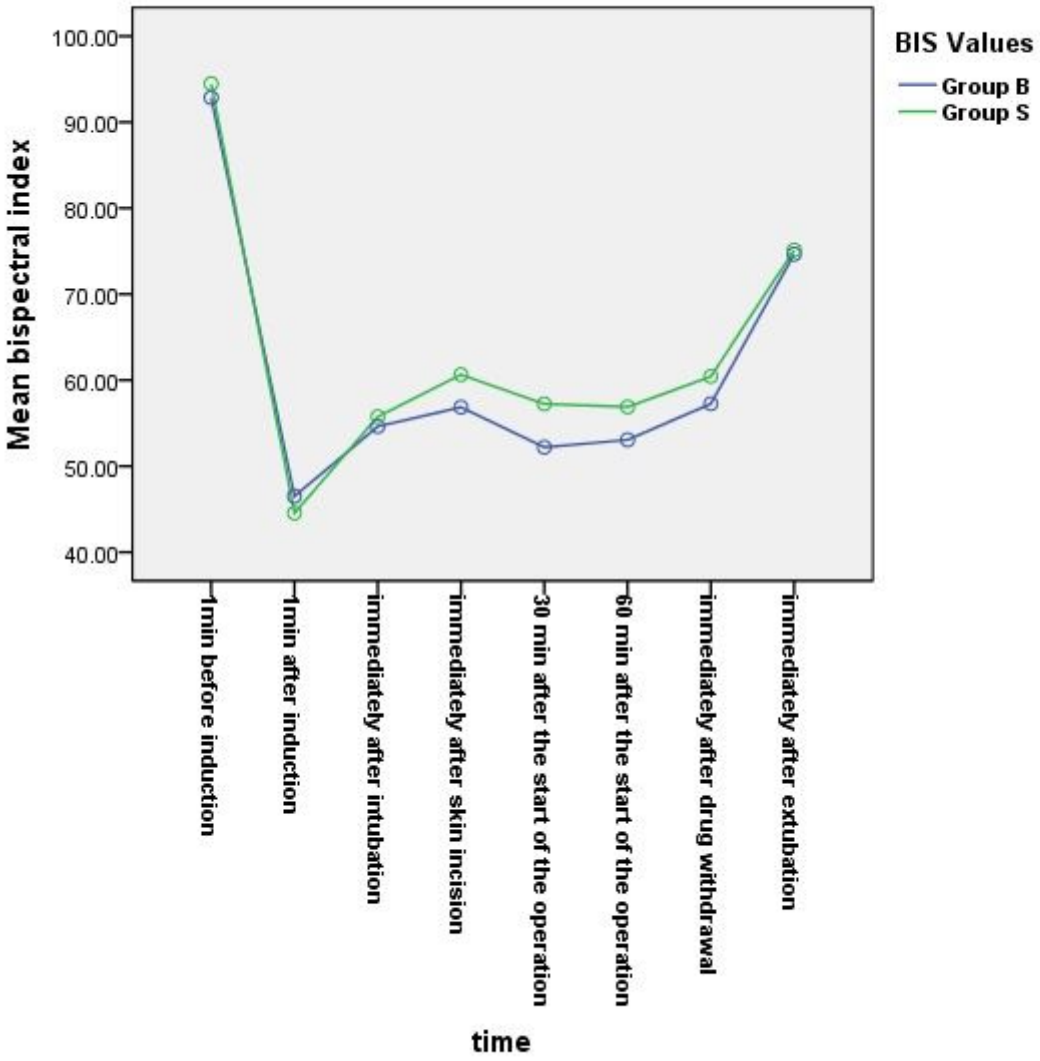

Figure 2

Changes in Bispectral Index (BIS) values at each time point in the two groups BIS values in the two groups were compared at 1 min before induction, immediately after skin incision, 30 min, and 60 min after the start of the operation, and immediately after drug withdrawal. BIS values in group S were higher than in group B, P>0.05.

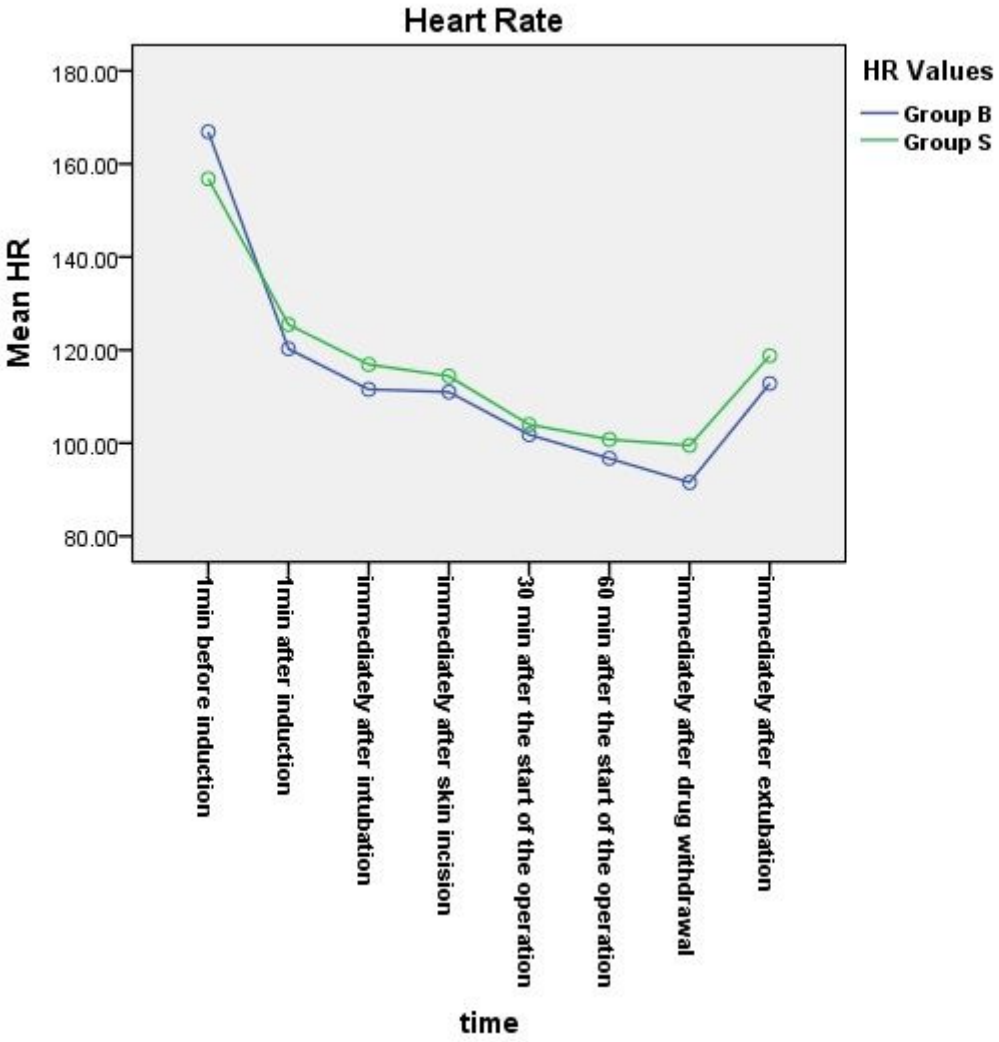

Figure 3

Changes in heart rates at each time point in the two groups There was no statistically significant difference in heart rate between groups, P>0.05.

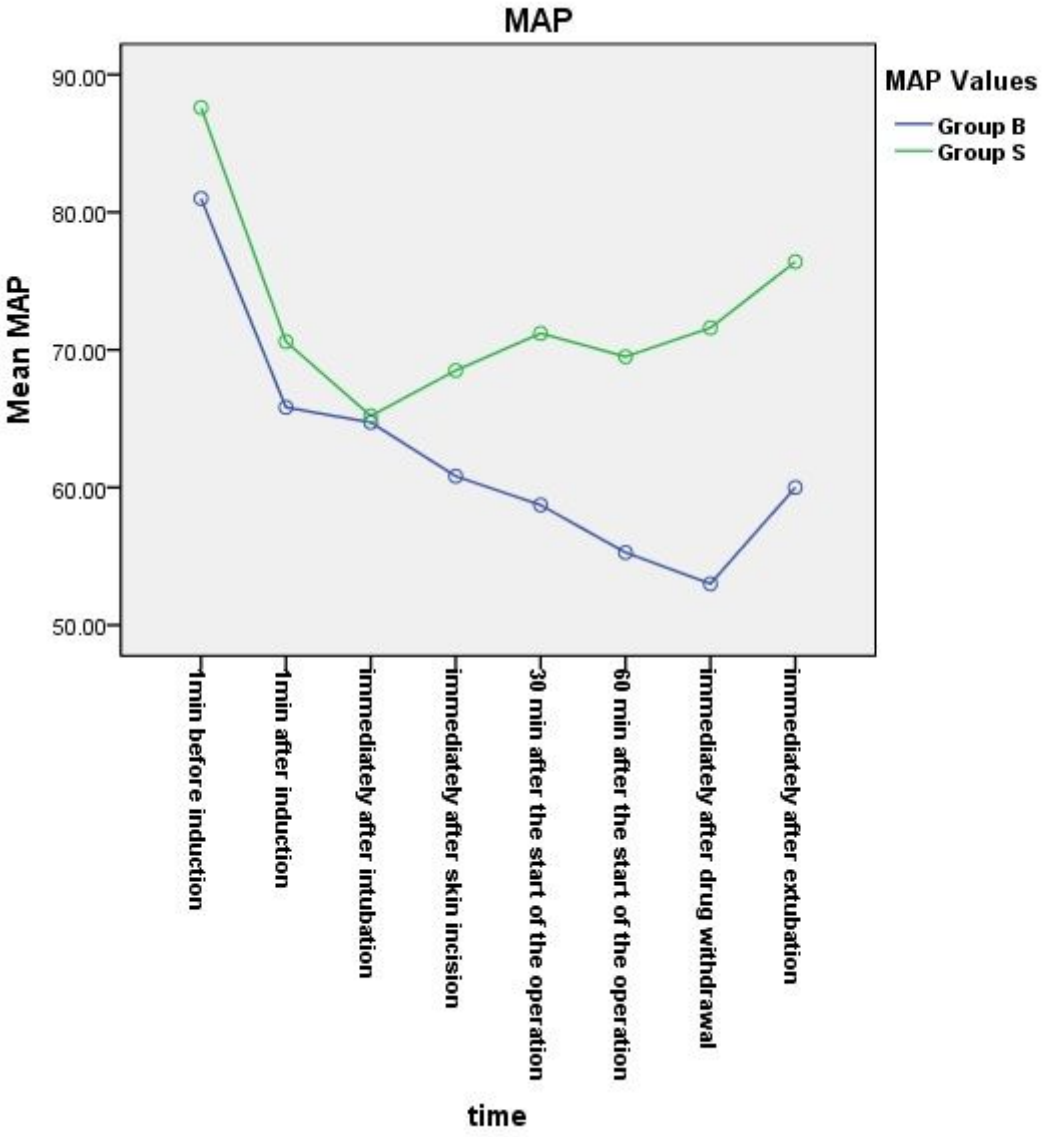

Figure 4

Mean arterial pressure (MAP) changes in the two groups There was a statistically significant difference in MAP between the two groups at 30 and 60 min after the start of the operation, immediately after drug withdrawal, and immediately after extubation; MAP in group B was lower than in group S, $P<0.05$.